To United States Patent and Trademark Office:

Re: U.S. Serial No. 10/542,885
Based on PCT/CN2004/000409

DECLARATION OF INVENTIOR

I, the undersigned, Xuehua Liu, declare and say:

1. I am a citizen of the People's Republic of China and I reside in Gongye Road West, Shaoguan, Guangdong, P.R.C.
2. I am a senior researcher at Li Min Pharmaceutical Factory of Livzon Pharmaceutical Group, and I have been doing researches relating to the art of Medicine and Pharmaceutics for more than 10 years.
3. I graduated in 2000 with a degree in Science from China Pharmaceutical University.
4. I am one of the co-inventors of the International Patent Application No. PCT/CN2004/000409 filed on 04/27/2004, entitled "The Saponin Family of Radix Notoginseng Intravenous Injection, A Method for Preparation Thereof", which is the International Publication of the present U.S. Patent Application Serial No. 10/542,885.
5. I am familiar with the field of pharmaceutics and pharmaceutical technology.
6. I am aware of and helped structure various tests conducted to assess the storage stability of pH and active concentration of the saponin family of Radix Notoginseng intravenous injection.
7. The tests are described in detail in Annex I and I will refer to the results obtained through the tests.
8. In my opinion, the presently claimed invention, as evidenced by the results shown in Annex I, indicates that the presently claimed saponin family of Radix Notoginseng intravenous injection exhibits relatively high storage stability in terms of pH and active concentration, as compared to the Xueshuantong injection as disclosed by Gai et al.
9. In my opinion, the presently claimed injection should not be obvious over the cited references, especially over the Xueshuantong injection as taught by Gai et al., because it has a better storage stability, that is surprising and unexpected.
10. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made may jeopardize the validity of

the application or any patent issued thereon.

Xuehua Liu 刘学华

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Date: Jan. 25, 2011

ANNEX I

I. Equipments and Reagents

1.1 Equipments

PH Meter: PHS-25 Type, commercially available from Shanghai REX Instrument Factory;

Ultraviolet Spectrophotometer: UV-2401PC Type, commercially available from Shimadzu Corporation;

Analytical Balance: TG-323A, made in China; BP-211D, made in Germany; and 92SM1202A, made in Switzerland.

1.2 Reagents

Perchloric Acid (AR): commercially available from Tianjin Dongfang Chemical Plant;

Glacial Acetic Acid (AR): commercially available from Guangzhou Chemical Plant;

Ginsenoside Rg1 (AR): Control, commercially available from Chinese National Institute for the Control of Pharmaceutical and Biological Products.

2. Methods

2.1 Measurement of PH Value

PH value is measured in accordance with *Pharmacopoeia of the People's Republic of China*, 2005 Edition.

2.2 Measurement of Total Saponins

2.2.1 Preparation of Control Solution:

Ginsenoside Rg1 was dried at a temperature of 60°C and a reduced pressure for 2 hours. 10 mg of ginsenoside Rg1 were accurately weighed, dissolved in absolute ethyl alcohol, transferred to a 100-ml volumetric flask, diluted to volume with absolute ethyl alcohol, and mixed uniformly. The resultant control solution contained 0.1 mg Rg1 per microliter.

2.2.2 Preparation of Sample Solution

2 ml of the i.v. injection of the present invention were accurately weighed in a 25-ml volumetric flask, diluted to volume with absolute ethyl alcohol, and mixed uniformly.

2 ml of Xueshuantong injection were accurately weighed in a 25-ml volumetric

flask, diluted to volume with absolute ethyl alcohol, and mixed uniformly.

2.2.3 Procedure of Measurement

2 ml of the control solution was placed into a test tube, dried up by evaporation in a water bath, and cooled to room temperature. 0.4 ml of a freshly formulated 5% solution of vanillin in glacial acetic acid and 1.6 ml of perchloric acid were added into the residues and mixed uniformly. The obtained solution was developed in a water bath at 60°C for 15 minutes, and then cooled to room temperature in an ice water bath. 10 ml of glacial acetic acid was added into the cooled solution and mixed uniformly. After standing for 10 minutes, measure the absorbance of the solution at the wavelength of 548 nm ± 3 nm in accordance with Annex VB of Volume 1 of *Pharmacopoeia of the People's Republic of China*, 2005 Edition.

Similar procedures as above were performed on the sample solution except that the control solution was replaced with the sample solution of the iv injection of the present invention or the sample solution of Xueshuantong injection.

Compare the absorbance of the sample solution and the control, and calculate accordingly the saponin amount contained in the iv injection of the present application or contained in Xueshuantong injection.

TABLE 1: ACCELERATED TEST FOR STORAGE STABILITY OF XUESHUANTONG INJECTION

Sample No.	Time (months)											
	0			1			2			3		
	pH	Conc. of Saponins (mg/ml)	Percent of the initial conc. of saponins	pH	Conc. of Saponins (mg/ml)	Percent of the initial conc. of saponins	pH	Conc. of Saponins (mg/ml)	Percent of the initial conc. of saponins	pH	Conc. of Saponins (mg/ml)	Percent of the initial conc. of saponins
1	5.84	1.41	100%	5.30	1.30	92.2	4.69	1.14	80.9	4.18	0.96	68.1
2	5.93	1.41	100%	5.42	1.31	92.9	5.17	1.16	82.3	4.60	1.04	73.8
3	5.98	1.41	100%	5.50	1.32	93.6	5.02	1.16	82.3	4.54	1.04	73.8
4	5.72	1.42	100%	5.26	1.30	91.5	4.90	1.15	81.0	4.08	0.96	67.6
5	5.87	1.40	100%	5.37	1.30	92.9	4.82	1.15	82.1	4.14	0.99	70.7
6	5.69	1.40	100%	5.08	1.29	92.1	4.76	1.15	82.1	4.00	0.95	67.9
7	5.74	1.41	100%	5.12	1.30	92.2	4.88	1.15	81.6	4.02	0.95	67.4
8	5.80	1.41	100%	5.44	1.31	92.9	5.10	1.16	82.3	4.23	0.99	70.2

TABLE 2. ACCELERATED TEST FOR STORAGE STABILITY OF THE PRESENTLY CLAIMED INJECTION

Sample No.	Time (months)											
	0			1			2			3		
	pH	Conc. of saponins (mg/ml)	Percent of the initial conc. of saponins	pH	Conc. of saponins (mg/ml)	Percent of the initial conc. of saponins	pH	Conc. of saponins (mg/ml)	Percent of the initial conc. of saponins	pH	Conc. of saponins (mg/ml)	Percent of the initial conc. of saponins
1	6.26	1.53	100	6.04	1.52	99.3	6.03	1.50	98.0	5.99	1.50	98.0
2	6.14	1.53	100	6.08	1.51	98.7	6.05	1.50	98.0	5.99	1.48	96.7
3	6.21	1.53	100	6.10	1.52	99.3	6.01	1.51	98.7	5.94	1.49	97.4
4	6.22	1.53	100	6.16	1.51	98.7	6.04	1.51	98.7	6.01	1.48	96.7
5	6.20	1.53	100	6.11	1.51	98.7	6.04	1.50	98.0	5.91	1.48	96.7
6	6.13	1.53	100	6.07	1.52	99.3	6.05	1.50	98.0	5.99	1.50	98.0
7	6.18	1.53	100	6.09	1.52	99.3	5.98	1.50	98.0	5.98	1.48	96.7
8	6.18	1.52	100	6.16	1.52	100	6.02	1.50	98.7	5.97	1.48	97.4

As shown in Table 1, the pH of Xueshuantong injection declines remarkably over time, especially after stored for 3 months, the pH even declines to a value which does not comply with the Chinese Medicine standard as taught in the last paragraph of the description. As a result, the concentration of the active ingredients, i.e., saponins, also exhibits a substantial declination over time. In particular, the concentration of active ingredients in Xueshuantong injection has decreased to less than 75% of the initial concentration after 3-month storage. Thus, it can be seen that the Xueshuantong injection has poor storage stability.

In contrast, it can be clearly seen from Table 2 that the IV injection prepared in accordance with the present invention exhibits superior storage stability. In particular, the product of the present invention exhibits a pH decrease of less than 0.3, while the concentration of saponins always keeps stable. In fact, the concentration of the active ingredients in the IV injection of the present invention remains more than 98% of the initial concentration after 3-month storage. Thus, the IV injection of the present invention was substantially improved in terms of storage stability of pH and active concentration, as compared with the Xueshuantong injection as taught by Gai et al.

Thus, the product of the present invention having better storage stability of pH and active concentration should not be obvious over the prior art including Xueshuantong injection because it produces surprise and unexpected effects.